

Atazanavir (ATV, Reyataz)

For additional information see Drugs@FDA:

<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>

Formulations

Capsules: 100 mg, 150 mg, 200 mg, and 300 mg

Dosing Recommendations

Neonate/infant dose:

ATV is not approved for use in neonates/infants. ATV should not be administered to neonates because of risks associated with hyperbilirubinemia (kernicterus).

Pediatric dose:

Data are insufficient to recommend dosing of ATV in all children younger than 6 years or in treatment-experienced children who weigh less than 25 kg.

For children ≥ 6 to < 18 years of age:

Weight (kg)	Once-Daily Dose*
Treatment-Naive ** Children Only	
15 to < 25 kg	ATV 150 mg + RTV 80 mg, both once daily with food
Both Treatment Naive and Treatment-Experienced Children	
25 to < 32 kg	ATV 200 mg + RTV 100 mg, both once daily with food
32 to < 39 kg	ATV 250 mg + RTV 100 mg, both once daily with food
≥ 39 kg	ATV 300 mg + RTV 100 mg, both once daily with food

* Higher doses than those currently recommended may be required for some patients. See discussion under [Pediatric Use](#).

** Data are insufficient to recommend this dose in treatment-experienced children who weigh less than 25 kg.

*For treatment-naive pediatric patients who do not tolerate ritonavir (RTV): **ATV boosted with RTV (ATV/r) is preferred for children and adolescents.***

Selected Adverse Events

- Indirect hyperbilirubinemia
- Prolonged electrocardiogram PR interval, first degree symptomatic atrioventricular (AV) block in some patients
- Hyperglycemia
- Fat maldistribution
- Possible increased bleeding episodes in patients with hemophilia
- Nephrolithiasis
- Skin rash
- Increased serum transaminases
- Hyperlipidemia (primarily with RTV boosting)

Special Instructions

- Administer ATV with food to enhance absorption.
- Because ATV can prolong the electrocardiogram (ECG) PR interval, use ATV with caution in patients with pre-existing cardiac conduction system disease or with other drugs known to prolong the PR interval (e.g., calcium channel blockers, beta-blockers, digoxin, verapamil).
- ATV absorption is dependent on low gastric pH; therefore, when ATV is administered with medications that alter gastric pH, special dosing information is indicated. (See [Drug Interactions](#) for recommendations on dosing ATV when the drug is coadministered with H2 receptor antagonists.) When administered with buffered didanosine (ddI) formulations or antacids, give ATV at least 2 hours before or 1 hour after antacid or ddI administration.
- The plasma concentration, and therefore therapeutic effect, of ATV can be expected to decrease substantially when ATV is coadmin-

Current Food and Drug Administration (FDA)-approved prescribing information does not recommend unboosted ATV in children younger than 13 years. If unboosted ATV is used in adolescents, higher doses than those used in adults may be required to achieve target drug levels (see [Pediatric Use](#)).

Adolescent (≥18–21 years of age)/adult dose:

Antiretroviral-naïve patients:

ATV 300 mg + RTV 100 mg or ATV 400 mg once daily with food. (If unboosted ATV is used in adolescents, higher doses than those used in adults may be required to achieve target drug levels [see [Pediatric Use](#)].)

Antiretroviral-experienced patients:

ATV 300 mg + RTV 100 mg, both once daily with food.

ATV in combination with efavirenz (EFV) (adults) in therapy-naïve patients only:

ATV 400 mg + RTV 100 mg + EFV 600 mg, all once daily at separate times.

Although ATV/r should be taken with food, EFV should be taken on an empty stomach, preferably at bedtime. EFV should not be used with ATV (with or without RTV) in treatment-experienced patients because EFV decreases ATV exposure.

ATV in combination with tenofovir (TDF) (adults):

ATV 300 mg + RTV 100 mg + TDF 300 mg, all once daily with food.

Only RTV-boosted ATV should be used in combination with TDF because TDF decreases ATV exposure.

istered with proton-pump inhibitors (PPIs). Antiretroviral therapy (ART)-naïve patients receiving PPIs should receive no more than a 20-mg dose equivalent of omeprazole, which should be taken approximately 12 hours before boosted ATV. Coadministration of ATV with PPIs is not recommended in treatment-experienced patients.

- Patients with hepatitis B virus (HBV) or hepatitis C virus (HCV) infections and patients with marked elevations in transaminases prior to treatment may be at increased risk of further elevations in transaminases or hepatic decompensation.

Metabolism

- ATV is a substrate and inhibitor of cytochrome P (CYP)3A4 and an inhibitor of CYP1A2, CYP2C9, and uridine diphosphate glucuronosyltransferase (UGT1A1).
- **Dosing of ATV in patients with hepatic impairment:** ATV should be used with caution in patients with mild-to-moderate hepatic impairment; consult manufacturer's prescribing information for dosage adjustment in patients with moderate impairment. ATV should not be used in patients with severe hepatic impairment.
- **Dosing of ATV in patients with renal impairment:** No dose adjustment is required for patients with renal impairment. However, ATV should not be given to treatment-experienced patients with end-stage renal disease on hemodialysis.

Drug Interactions (See also the [Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents](#)):

- **Metabolism:** Atazanavir is both a substrate and an inhibitor of the CYP3A4 enzyme system and has significant interactions with drugs highly dependent on CYP3A4 for metabolism. Atazanavir also competitively inhibits CYP1A2 and CYP2C9. There is potential for multiple drug interactions with atazanavir. Atazanavir inhibits the glucuronidation enzyme UGT1A1. Atazanavir is a weak inhibitor of CYP2C8.
- Before atazanavir is administered, the patient's medication profile should be carefully reviewed for potential drug interactions with atazanavir.
- **Nucleoside reverse transcriptase inhibitors (NRTIs):** Tenofovir decreases atazanavir plasma concentrations. Only ritonavir-boosted atazanavir should be used in combination with tenofovir.

- *Non-nucleoside reverse transcriptase inhibitors (NNRTIs)*: Efavirenz, etravirine, and nevirapine decrease atazanavir plasma concentrations significantly. Nevirapine and etravirine should not be coadministered to patients receiving atazanavir (with or without ritonavir). Efavirenz should not be coadministered with atazanavir in treatment-experienced patients but may be used in combination with atazanavir 400 mg plus ritonavir boosting in treatment-naïve adults.
- *Absorption*: Atazanavir absorption is dependent on low gastric pH. When atazanavir is administered with medications that alter gastric pH, dosage adjustment is indicated. No information is available on dosing atazanavir in children when the drug is coadministered with medications that alter gastric pH.

Guidelines for dosing atazanavir with antacids, H₂ receptor antagonists, and PPIs in adults are as follows:

- *Antacids*: Atazanavir concentrations are decreased when the drug is coadministered with antacids and buffered medications (including buffered didanosine formulations); therefore, atazanavir should be administered 2 hours before or 1 hour after these medications.
- *H₂-Receptor Antagonists (unboosted atazanavir in treatment-naïve patients)*: H₂ receptor antagonists are expected to decrease atazanavir concentrations by interfering with absorption of the ARV agent. Atazanavir 400 mg should be administered at least 2 hours before or at least 10 hours after a dose of the H₂ receptor antagonist. (A single dose of an H₂ receptor antagonist should not exceed a dose comparable to famotidine 20 mg; a total daily dose should not exceed a dose comparable to famotidine 40 mg.)
- *H₂-Receptor Antagonists (boosted atazanavir in treatment-naïve or -experienced patients)*: H₂ receptor antagonists are expected to decrease atazanavir concentrations by interfering with absorption of the ARV. Dose recommendations for H₂ receptor antagonists are either a ≤ 40 -mg dose equivalent of famotidine twice daily for treatment-naïve patients or a ≤ 20 -mg dose equivalent of famotidine twice daily for treatment-experienced patients. Boosted atazanavir (ATV 300 mg + RTV 100 mg) should be administered simultaneously with and/or ≥ 10 hours after the dose of H₂ receptor antagonist.
- *H₂-Receptor Antagonists (boosted atazanavir with tenofovir)*: Treatment-experienced patients using both tenofovir and H₂-receptor antagonists should be given an increased dose of atazanavir (ATV **400 mg** + RTV 100 mg + TD F 300 mg).
- *PPIs*: Coadministration of PPIs with atazanavir is expected to substantially decrease atazanavir plasma concentrations and decrease its therapeutic effect. Dose recommendations for therapy-naïve patients are ≤ 20 -mg dose equivalent of omeprazole taken approximately 12 hours prior to boosted atazanavir (ATV 300 mg + RTV 100 mg). Coadministration of atazanavir with PPIs is not recommended in treatment-experienced patients.

Major Toxicities:

- *More common*: Indirect hyperbilirubinemia that can result in jaundice or icterus but is not a marker of hepatic toxicity. Headache, fever, arthralgia, depression, insomnia, dizziness, nausea, vomiting, diarrhea, and paresthesias.
- *Less common*: Prolongation of PR interval of electrocardiogram. Abnormalities in AV conduction generally limited to first-degree AV block, but with rare reports of second-degree AV block. Rash, generally mild to moderate, but in rare cases includes life-threatening Stevens-Johnson syndrome (SJS). Fat maldistribution and lipid abnormalities may be less common than with other protease inhibitors (PIs). However, the addition of ritonavir to atazanavir is associated with lipid abnormalities but to a lesser extent than with other boosted PIs.

- *Rare:* New onset diabetes mellitus, hyperglycemia, ketoacidosis, exacerbation of pre-existing diabetes mellitus, spontaneous bleeding in hemophiliacs, and elevation in serum transaminases. Nephrolithiasis. Hepatotoxicity (patients with hepatitis B or hepatitis C are at increased risk).

Resistance: The International Antiviral Society-USA (IAS-USA) maintains a list of updated resistance mutations (see http://www.iasusa.org/resistance_mutations/index.html) and the Stanford University HIV Drug Resistance Database offers a discussion of each mutation (see <http://hivdb.stanford.edu/pages/GRIP/ATV.html>).

Pediatric Use: Atazanavir is FDA approved for use in children and adolescents. Ritonavir-boosted atazanavir is generally preferred over unboosted atazanavir and is used in combination with NRTIs for treatment in children who are ≥ 6 years of age.

The results of the IMPAACT/PACTG 1020A trial in children and adolescents indicate that, in the absence of ritonavir boosting, atazanavir can achieve protocol-defined pharmacokinetic (PK) targets, but only when used at higher doses of atazanavir (on a mg-per-kg body weight or mg-per-meter² body surface area basis) than doses currently recommended in adults. In IMPAACT/PACTG 1020A, children older than 6 and younger than 13 years of age required atazanavir dosing of 520 mg per meter² of body surface area per day of atazanavir capsule formulation to achieve PK targets. Doses required for older adolescents were greater than the adult approved dose of 400 mg atazanavir given without ritonavir boosting once daily: adolescents >13 years of age required atazanavir dosing of 620 mg per meter² of body surface area per day¹. In this study, the areas under the curve (AUCs) for the unboosted arms were similar to the ritonavir-boosted atazanavir groups but the maximum plasma concentration (C_{\max}) was higher and minimum plasma concentration (C_{\min}) lower for the unboosted arms. Median doses of atazanavir in mg/m² body surface area both with and without ritonavir boosting from IMPAACT/PACTG 1020A are outlined in the following table. When dosing unboosted atazanavir in pediatric patients, therapeutic drug monitoring (TDM) is recommended to ensure that adequate atazanavir plasma concentrations have been achieved. A minimum target trough concentration for atazanavir is 150ng/mL². Higher target trough concentrations may be required in PI-experienced patients.

Summary of ATV Dosing Information Obtained from IMPAACT/PACTG 1020A¹

Age range (years)	Was ATV given with RTV Boosting?	ATV median dose (mg/m ² *)	ATV median dose (mg*)
6–13 years	No	509	475
6–13 years	Yes	208	200
>13 years	No	620	900
>13 years	Yes	195	350

*Dose satisfied protocol-defined AUC/PK parameters and met all acceptable safety targets. These doses differ from those recommended by the manufacturer. TDM was used to determine patient-specific dosing in this trial.

Regarding toxicity, 8.5% (11 of 129) of patients enrolled in the trial had a bilirubin >5 times the upper limit of normal. Asymptomatic ECG abnormalities were observed in a small number of patients: Grade 3 QTC prolongation in 1 patient, Grade 2 PR or HR changes in 9 patients, and Grade 3 PR prolongations in 3 patients. No significant changes in serum cholesterol or triglycerides (TGs) were observed during 48 weeks of therapy in 63 children receiving unboosted atazanavir in combination with 2 NRTIs³⁻⁴.

In a small single site study, 23 pediatric patients (median age 16 years) on combination antiretroviral therapy (cART) were switched to a once-daily ritonavir-boosted atazanavir-containing regimen because of virologic failure (12 patients) or for treatment simplification (11 patients)⁵. Twenty of the patients had previously received PI-based regimens with the median number of 2 atazanavir mutations acquired prior to switching to ATV/r. Patients received atazanavir doses lower than those currently recommended and many patients received concomitant therapy with tenofovir and/or didanosine. Both tenofovir and didanosine are known to have PK interactions with atazanavir. In this study, atazanavir plasma concentrations were measured at 12–15 hours after dosing: 6 patients had undetectable levels at multiple time points, and considerable interpatient variability in plasma atazanavir concentrations was noted. Four of the 13 patients who previously had undetectable viral loads experienced virologic failure; 6 of 12 patients who previously had virologic failure achieved undetectable viral loads.

References

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